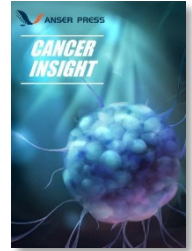




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How Does Lncrna Regulation Impact Cancer Metastasis

Abreto Devit Mancheng ^a, Ugwemubwem Ossas ^{a*}

^a *Internal Medicine, Hopital du Mali, Bamako, Mali.*

ABSTRACT

Metastasis is the major cause of cancer-related mortality. Metastasis is a process through which cancer spreads from its initial location to other sections of the body. Cancer cells' epithelial-mesenchymal transition (EMT), anoikis resistance, cell migration, and angiogenesis are all well-known steps in this process. Investigating the molecular processes that govern cancer metastatic progression may lead to more effective diagnostic and treatment strategies. Long non-coding RNAs (lncRNAs) have recently discovered to have a vital more than 200 nucleotides. A rising body of research indicates that lncRNAs have a role in a wide range of biological processes and diseases, including cancer. The usage of lncRNA in cancer metastasis has been widely researched. However, according to current studies, lncRNA is mostly associated with the EMT process. This review focuses on the processes behind lncRNA involvement in cancer metastasis.

KEYWORDS: Noncoding RNAs (ncRNAs); Long noncoding RNAs (lncRNAs); Cancer metastasis; Gene regulation

1. Introduction

*Corresponding author: Ugwemubwem Ossas

E-mail address: Ossas@gmail.com

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Cancer metastasis is a challenging process that occurs when a tumour spreads from its initial location to another section of the body [1]. According to previous research, 60 to 70% of cancer patients develop metastases before they are diagnosed. Cancer patients die most often from metastasis. Tumor cells enter the cancer metastasis process due to a variety of biological causes. Non-coding RNAs like long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) may have a role in cancer metastasis, in addition to genes that code for proteins [2,3]. There have been a number of studies on miRNAs and cancer metastasis [4,5]. The characters of lncRNAs in cancer metastasis is the subject of this review. lncRNA is a non-protein coding RNA molecule with a low level of conservation that may affect gene expression by histone modification, transcription, and/or post-transcriptional regulation. Interacting proteins, DNA, and RNA make use of them as activators, decoys, guides, and scaffolds [6,7]. A rising amount of evidence implies that long noncoding RNA is involved in almost every biological activity, including stem cell proliferation, cell maintenance, cell infiltration, and metastasis [8-10]. lncRNA has a role in virtually all human malignancies, according to growing evidence (**Figure 1**). The lncRNA HOX transcript antisense RNA (HOTAIR) has been extensively investigated, and its expression in breast cancer patients has been shown to significantly predict death and cancer metastasis. The connection of HOTAIR with Polycomb Repressive Complex 2 (PRC2) may change the cell expression profile linked to cancer metastasis and improve breast cancer metastasis [11]. HOTAIR has been shown to be overexpressed in liver, colon, pancreatic cancer, and gastrointestinal stromal tumours, and to aid in the spread of these cancers [12-15]. The study of translocation-related lncRNAs is a unique tool that might help us better understand the molecular processes that control the translocation cascade. The usage of lncRNAs in cancer metastasis is the topic of this review.

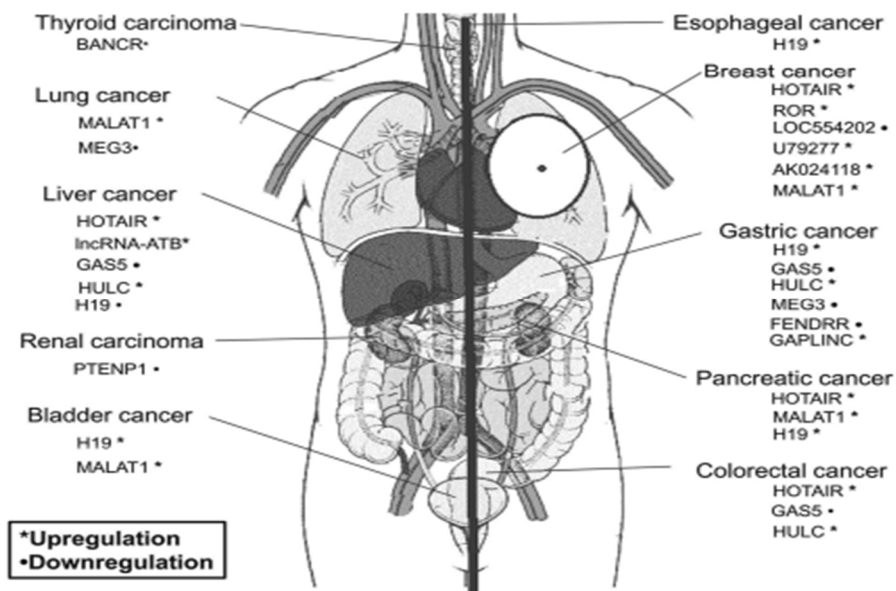


Figure 1. lncRNAs may be involved in almost all the human cancers.

2. Regulation of lncRNAs

2.1 lncRNA transcriptional regulation

Thanks to the introduction of high-throughput genomic technologies like RNA sequencing and lncRNA microarrays, many lncRNAs have been discovered in recent years. Little is known about the transcriptional regulation of the lncRNA gene due to the high false-positive rate of the lncRNA transcription factor binding site prediction approach. Many databases have been constructed to unravel the transcriptional regulation of lncRNAs based on theChIPSeq peak list of ENCODE transcription factors. (<http://tf2lncrna.mlg.hit.edu.cn>; <http://deepbase.sysu.edu.cn/chipbase/>). The hypothesised transcription factors of lncRNA must be confirmed.

3. Methylation of DNA

lncRNAs are regulated. Increasing evidence suggests that the DNA methylation and lncRNAs regulatory network interact. Dppa2 is epigenetically mutated in cis by Dum, a lncRNA that activates the methylation enzymes Dnmt1, Dnmt3a, and included Dnmt3b. Furthermore, epigenetic alterations in cancer have been shown to de-regulate numerous lncRNAs. We all know that imprinted genes are critical for embryonic development and are controlled by DNA methylation of maternal or paternal alleles. Many lncRNAs, such as MEG3 and H19, are imprinted genes. A differentially methylated region (DMR) in the H19 promoter is methylated in various ways depending on paternal inheritance. DNA methylation normally silences the paternal allele of H19, while DNA unmethylation activates the maternal allele. H19 is overexpressed in a variety of human malignancies, like bladder cancer, esophageal cancer, lung cancer, breast cancer, [16-21] due to DNA methylation control. Aside from H19, tumor-suppressive lncRNAs such as Maternally Expressed Gene 3 (MEG3) [22-25] and long non-coding RNA (LOC554202) are downregulated in a variety of malignancies owing to promoter CpG methylation [26,27]. NBAT1 (neuroblastoma-associated transcript1) was investigated as a neuroblastoma biomarker, and CpG methylation was shown to influence NBAT1 expression [28]. Due to abnormal DNA methylation, lncRNA works as an epigenetic regulator of gene expression in some cancers. Hypermethylation of the tumour suppressor gene lncRNA and hypomethylation of the on-colon cRNA both promote cancer development.

3.1 Cancer metastasis and lncRNAs

Transcript 1 of lung adenocarcinoma with metastasis (MALAT1) MALAT1 was linked to a extremely low prognosis in individuals with early-stage non-small cell lung cancer, and it had a high proclivity for spreading [29]. The expression of MALAT1 is upregulated in a variety of human cancers, including colon, pancreatic, prostate, glioma, and bladder cancer [30-35]. MALAT1 dysregulation has been associated to HPV infection in cervical cancer, and MALAT1 might be involved in invasion and cervical cancer cell proliferation [36]. When epithelial cells lose their features and turn into invasive mesenchymal cells and migratory, this is known as the epithelial-mesenchymal transition (EMT). TGFb, an EMT activator, promotes MALAT1 expression in bladder cancer cells [37]. MALAT1 binds to the suppressor Zest 12 (SUZ12), lowering cadherin expression

while enhancing cadherin and fibronectin expression. Another research found that MALAT1 activated Wnt signalling in bladder cancer, causing EMT and cancer metastasis [34]. MALAT1 is upregulated in both lung and bladder cancers, and it promotes lung cancer brain metastasis via activating EMT [38]. MALAT1 plays an important function in cancer dissemination through EMT. MALAT1's function in cancer migration and invasion might be mediated by other routes. According to Miyagawa et al., MALAT1 may regulate gene expression in HeLa cells at the transcriptional and/or post-transcriptional stages [39]. Many studies have linked MALAT1 to the regulation of alternative splicing by modulating the quantities of active serine/arginine (SR) splicing proteins [40]. It's yet unclear how it influences tumour metastasis.

3.2 Antisense intergenic RNA (HOX) (HOTAIR)

HOTAIR, a non-coding RNA that is overexpressed in metastatic breast cancer and is discovered on chromosome 12 of mammals [41]. HOTAIR overexpression in hepatocellular carcinoma recurrence risk after liver transplantation has risen [42]. HOTAIR might be a new prognostic marker for non-small cell lung cancer, esophageal squamous cell carcinoma, endometrial cancer, and cervical cancer [43-46]. Gastric cancer cells can have their invasiveness reduced and their Emergency Medical Technicians (EMT) process reversed by knocking down HOTAIR [47]. HOTAIR has been connected to gene expression as well as the PRC2 complex, which regulates H3K27 methylation. HOTAIR acts as a guide for interacting with PRC2, resulting in the retargeting of the Packed Red Cells (PRC2) complex throughout the genome [48]. PRC2 was redirected to silence the HOXD gene on chromosome 2 of mammary epithelial cells. According to further studies, HOTAIR seems to function not only as a guide by binding to PRC2, but also as a molecular scaffold by adhering to at least two different histone-modified complexes. HOTAIR regulates H3K27 methylation and H3K4 demethylation through binding to PRC2 and the LSD1 complex [49]. In a nutshell, HOTAIR may control the epigenome of cancer by binding to histone-modified complexes and reprogramming chromatin states to promote cancer progression.

3.3 H19

H19, a 2.3-kilobyte RNA product with no protein coding sequence [50]. RNA polymerase II transcribes, splices, and polyadenylates it. The H19 gene, an imprinted gene that can only be expressed by one parent [51]. H19 levels are elevated in many types of cancer, including stomach cancer, serous ovarian cancer, esophageal cancer, bladder cancer, breast cancer, and lung cancer [52-58]. H19 is associated with cancer metastasis, most probably through miRNA antagonism or epigenetic regulation of EMT development [59]. H19 is a precursor of miR675, and some EMT inducers increase the expression of both H19 and miR675 [60-62]. TGF β enhanced Slug, H19, and miR675 through the PI3K/AKT pathway [63]. H19 expression was significantly increased in primary pancreatic ductal adenocarcinoma (PDAC) that later metastasized. H19 increased HMGA2 expression, which has been connected to EMT, and boosted PDAC cell infiltration and migration by inhibiting let. H19 levels are greatly raised in bladder cancer tissue, and H19 might be employed as a diagnostic for bladder cancer development [64]. Another research discovered that via connecting to the Zesthomolog 2 (EZH2) enhancer, H19

may increase Wnt/bcatenin signalling and decrease e-cadherin synthesis in bladder cancer cells [65, 66]. H19 may aid in cancer metastasis, which directly influences the EMT process. H19, on the other hand, has been demonstrated to be downregulated in HCC tissue and to predict the disease's outcome. H19 inhibits the production of EMT markers via activating the miR200 family, hence preventing HCC metastasis [67]. H19 may also have increased histone acetylation in conjunction with the hnRNP U / PCAF / RNAPol II protein complex, leading in the activation of miR200 expression [68]. H19's unusual expression pattern might be attributed to tissue specificity, and the underlying mechanism of H19's aberrant expression must be investigated further. LncRNAs, like miRNAs, may play a number of roles in cancer through a variety of mechanisms. As a result, knowing the role of lncRNA in carcinogenesis is critical.

3.4 Specific Growth Arrest 5 (GAS5)

GAS5 is a long noncoding RNA (lncRNA) found in mouse genomic DNA that may be a tumour suppressor gene that is highly expressed in cells that have achieved saturation density [69]. T [1; 3] (q25; q27) may induce GAS5 to join with the Bcl6 gene in B-cell lymphoma [70]. GAS5 is a prognostic biomarker for cervical cancer, colorectal cancer, hepatocellular carcinoma, and gastric cancer [71-74]. GAS5 has been identified as a tumour suppressor gene in many malignancies, however the mechanism by which it contributes to carcinogenesis is unclear. Recent study has connected GAS5-related snoRNA levels to p53 expression and DNA damage in colorectal cancer [75]. GAS5's main function in cancer is cell death, and until recently, no study on the role of GAS5 in cancer spread has been done.

3.5 Maternal expression number three (MEG3)

MEG3 is an imprinted maternal allele-expressed lncRNA gene. This gene is imprinted by the methylation-regulated binding protein CTCF of cytosine [76]. MEG3 is silenced in many cancer cells due to DNA methylation [77-79]. MiR29 and miR148 may regulate DNA methyltransferases 1 and 3 in hepatocellular carcinoma and gastric cancer, enhancing MEG3 expression [80, 81]. MEG3 has a poor prognosis for stomach cancer, pituitary adenoma, tongue squamous cell carcinoma, and lung cancer [82-84]. We observed that decreased MEG3 expression was connected to a lower histological grade and deeper tumour infiltration in colorectal cancer [85]. The basic mechanism of MEG3 cancer metastasis, however, is unclear. According to further study, MEG3 may inhibit tumour formation through p53-dependent and/or p53-independent pathways [86].

3.6 Highly upregulated in liver cancer (HULC)

Highly upregulated in liver cancer (HULC) was initially identified in hepatocellular carcinoma, but it has since been found in colorectal cancer that has spread to the liver [87,88]. IGF2 mRNA-binding protein 1 (IGF2BP1) may have a post-transcriptional effect in HULC expression [89]. The PKA signalling pathway or the transcription factor CREB elevated HULC levels in liver cancer. By binding to numerous miRNAs, including miR372, the upregulated HULC acts as an endogenous sponge [90]. MiR372 inhibits PRKACB kinase translation by

increasing PRKACB levels. PRKACB activates CREB by phosphorylating HULC and increasing its expression. The HULCmiR372 PRKACB-CREB-HULC regulatory loop is critical in cancer metastasis. According to Zhao et. al suppressing HULC successfully reverses the EMT phenotype of human colon cancer [91]. lncRNARoR is a noncoding RNA that directly interacts with both the heterogeneous ribonuclear protein I (hnRNP I) to inhibit p53 translation. [92,93]. mlncRNAROR's primary job was to keep embryonic stem alive with induced pluripotent stem cells (iPSCs) as well as to play a role in carcinogenesis [94]. According to our results, ROR influences EMT development in human breast epithelial cells by functioning as a competing endogenous RNA for miR205 [95]. Triple-negative breast cancer (ER-, HER2-, and PR-) has a poor prognosis due to a paucity of therapy options. The absence of miRNA145 might be an indication of TNBC. TNBC contains a very high amount of RoR, which competes as an endogenous RNA sponge with miR145. ARF6, a miR145 target gene, regulates breast cancer cell invasion and metastasis. ARF6 affects cell-cell adhesion by changing ecadherin location [96]. TNBC metastasis is governed by the miR145 signalling pathways, according to these results. lncRNAROR, in other words, is largely a competitive endogamymiRNA sponge that encourages tumor spreading.

3.7 Additional lncRNAs

TGF β activates lncRNAATB, which was discovered in hepatocellular cancer metastases (HCC). lncRNAATB may promote cancer cell migration by competitively binding to the miR200 family. MiR200 has the capacity to suppress the expression of EMT inducers ZEB1 and ZEB2. lncRNAATB enhances cancer cell invasion by triggering EMT. Furthermore, by binding to IL11 mRNA and activating the STAT3 signalling pathway, lncRNAATB may increase the organ colonisation of disseminated tumour cells [97,98]. PTENP1 is a pseudogene of the PTEN tumour suppressor gene [99]. DNA methylation reduces PTENP1 expression in clear cell renal cell cancer (ccRCC) [100]. PTENP1 has been deleted from human melanoma [101]. PTEN P1 and PTEN are direct targets for miR21 in the ccRCC cell line, and miR21 reduces their activity [102]. PTEN P1 and PTEN expression in tissues are both negatively associated with miR21 expression. Patients with ccRCC who lacked PTENP1 had a worse chance of survival. PTENP1 expression in cells expressing miR21 inhibits cell proliferation, invasion, tumour development, and metastasis, mimicking PTEN expression. The lncRNA LOC554202 encodes the miR31 host gene. Because to promoter methylation, both miR31 and LOC554202 are down regulated in TNBC cell lines. Inhibiting Loc554202 may reduce breast cancer cell migration and invasion. lncRNA expression profiling found BC040204, U79277, AK024118, and AK000974, and their expression is linked to breast cancer patient survival times [103]. The lncRNA FENDRR regulates heart and body development in mice [104]. This lncRNA was shown to be downregulated in gastric cancer tissues owing to histone deacetylation, and it was linked to tumour invasion and lymphatic metastasis. FENDRR has been shown to reduce the expression of metastasis-related genes FN1 and MMP2/MMP9, hence preventing gastric cancer cell invasion and migration [105]. GAPLINC (gastric adenocarcinoma predictive long intergenic noncoding RNA) overexpression is identified in gastric cancer tissues and is associated with a subset of individuals who have a bad prognosis. GAPLINC regulates CD44 as a molecular decoy for miR211, a microRNA that targets both CD44 and GAPLINC, according to mechanistic study [106,107]. In cervical cancer, lncRNAEBIC (EZH2binding lncRNA in

cervical cancer) was shown to be increased. By binding to EZH2, LncRNAEBIC may increase cervical cancer cell motility and invasion. EBIC/EZH2, a critical molecule in the spread of cervical cancer, suppresses E-cadherin expression [108].

4. In cancer metastasis, lncRNA and miRNA interact

LncRNA breakdown caused by miRNA Both miRNA and lncRNA are non-coding RNAs, and miRNAs influence the abundance of numerous lncRNAs (**Figure 2A**). According to recent research, miRNAs can influence more than one-third of the genes that code for proteins by attaching to the 3' untranslated region (UTR). MiRNAs target lncRNAs and potentially disrupt them, according to new study. In human cancer, the let-7 (let7) gene family was first identified as a key developmental regulator, and it is a direct regulator of the oncogene RAS [109]. In addition to the Ras gene, Let7 can regulate lncRNA. H19 is controlled by the Let7 genes (let7a, let7b, let7g, and let7i) [110,111]. Another lncRNA HOTAIR is downregulated by Let7, and this regulation is transmitted to the RNA-binding protein HuR. This demonstrates that lncRNA disruption caused by HuR-enhanced-microRNA interactions is widespread. Another well-studied miRNA, MiR21, has been shown to be an oncogene in a variety of malignancies [112]. Zhang. We observed that miR21 controls lncRNA GAS5 through RNA-induced silencing complex (RISC) pathways in breast cancer cells [113]. MiR9 targets MALAT1, a lncRNA that also includes RISC [114]. Gene regulation is aided by non-coding RNAs such as lncRNA and miRNA. Understanding the interactions between microRNAs and long noncoding RNAs provides insight into the underlying mechanisms of several aspects of the tumour process, such as metastasis.

4.1 lncRNA reservoir for miRNA

Several lncRNAs contribute to cancer spread by producing miRNAs (**Figure 2B**). In mice, HuR inhibits H19's production of miR675 [115,116]. By generating miR675, H19 may aid in the spread of cancers such as glioma, gastric cancer, and prostate cancer [117,118]. Decreased expression of miR675 and H19 on the other hand, may increase the motility and invasion of human hepatocellular carcinoma cells. Similarly, lncRNA LOC554202 may encode miR31, and promoter methylation of lncRNA LOC554202 reduces miR31, facilitating breast cancer invasion and metastasis [119]. LincMD1 synthesises MiR206 and MiR133b from introns and exons, respectively. MiR206 could be able to block breast cancer cells from migrating by directly targeting coronin 1C, an actin-binding protein [120]. MiR133b may be a novel prognostic marker for colorectal cancer in humans [121]. All of these results point to the possibility that certain lncRNAs act as miRNA reservoirs and may have a dual regulatory role. In addition to producing miRNAs, lncRNA has the potential to influence miRNA production. Liz *et al.* discovered that the lncRNA Uc.283+A impacted premiRNA195 maturation at the Drosha processing level [122].

4.2 lncRNAs are miRNA sponges

lncRNAs may create miRNAs and compete with miRNAs for mRNA binding (**Figure 2C**). When miRNAs bind to them, they may either cause lncRNA degradation or act as a miRNA sponge. lncMD1 increased MAML1 and MEF2C mRNA expression, while miR135 encouraged muscle growth in murine and human myoblasts by acting as an endogenous sponge for miR133 [123]. It has been shown that HULC acts as a miRNA sponge, facilitating the spread of hepatic cancer. By sequestering miR200s, lncRNAATB may promote EMT in liver cancer. PTENP1 is a pseudogene of the tumour suppressor gene PTEN, and the three untranslated regions (UTRs) for the same miRNAs are equivalent. By competing with endogenous RNA, PTENP1 may reduce the effect of PTEN posttranscriptional inhibition. Mutations in the 3' UTR of PTENP1 may impact PTEN expression in human melanoma, leading to cancer spread.

Finally, data suggest that lncRNAs and miRNAs collaborate to impact gene expression through complicated posttranscriptional pathways. All of these findings emphasised the growing complexities of ncRNA-mediated regulation networks. More instances of lncRNAs regulating expression of genes via competition or collaboration with miRNAs are anticipated to emerge. MicroRNAs and long noncoding RNAs work together to limit tumor spread in a powerful and dynamic way.

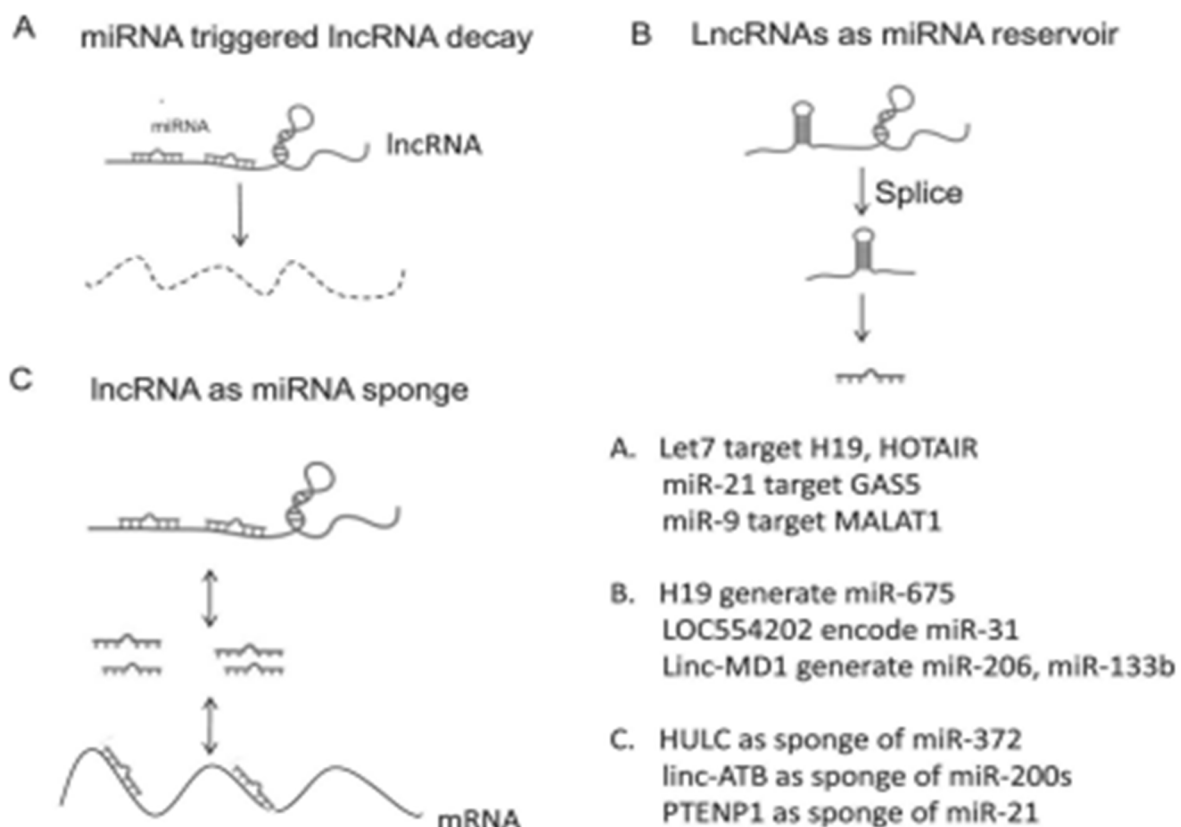


Figure 2. miRNA interactions and lncRNA in cancer metastasis. (A) MiRNAs control the expression of a large number of lncRNAs and cause their degradation. (B) lncRNAs are capable of producing miRNAs. (C) Long noncoding RNAs may compete for mRNA binding with miRNAs.

5. lncRNA as a cancer diagnostic and therapeutic target

Cancer is among the illnesses that has a significant risk of mortality due to metastasis. It is challenging to identify early targets for diagnosis and therapy of this illness. Personalised medicine has entered the age of cancer with the arrival of molecular mechanism research. Due to a better knowledge of the molecule's alterations, a more accurate and relevant cancer diagnostic and prognostic sign is on the horizon. Epigenetic alterations such as histone modification DNA methylation, lncRNA and microRNA expression, in associated with genetic changes, may give crucial clinical information. lncRNA may operate as an epigenetic regulator in gene regulation at the transcriptional or posttranscriptional levels, and it may be used to identify and cure cancer. Numerous studies have shown that lncRNAs are incorrectly regulated in a range of malignancies and are linked to cancer metastasis. lncRNAs might be used as potential biomarkers to detect and treat cancer. Many lncRNAs have been identified as cancer diagnostic biomarkers using lncRNA arrays or RNA sequencing. TGF β reactivated lncRNAATB in HCC, and lncRNAATB expression was associated with prognosis. Higher HOTAIR levels have been associated to an increased risk of recurrence following liver transplant. GAPLINC overexpression is associated with a poor prognosis in a subgroup of gastric cancer patients. All of these lncRNAs have been found in tumour tissue, and their expression is linked to cancer patient prognosis. lncRNAs, like circulating miRNAs, may be found in cancer patients' blood, sputum, and urine. The lncRNA DD3, which is solely expressed in the prostate, has been developed as a prostate cancer marker with more specificity than prostate-specific serum antigen (PSA) [124-126]. Similarly, the lncRNA HULC, which is strongly expressed in liver cancer, has been discovered in cancer patients' blood. These noninvasive cancer diagnostic targets might be long noncoding RNAs (lncRNAs). The use of lncRNAs as cancer therapeutic targets is still in its infancy [127]. Although the specific role of lncRNA in cancer is unknown, certain lncRNAs may be used as targeted therapies.

When several lncRNAs connect to a protein complex, they may create a secondary structure and play crucial functions; this might be a way to intervene [128]. HOTAIR controls gene expression by interacting with the PRC2 or LSD1 complex. By preventing this binding, breast cancer cells are less likely to propagate [129]. lncRNAs have the potential to behave as tumour suppressors or oncogenes via interacting with DNA, miRNAs, and proteins. TGS, or RNA-induced transcriptional gene activation, has been proposed as a potential treatment method [130]. Many human malignancies have dysregulated lncRNA, which might be a therapeutic target for transgene-mediated therapy. H19 is one of these lncRNAs that is overexpressed in a range of malignancies [131]. H19 expression is being actively researched, notably in the therapy of bladder cancer. The diphtheria toxin A gene is found on BC819, a double-stranded DNA plasmid driven by the H19 promoter sequence.

The majority of clinical studies for bladder cancer treatment have focused on the effectiveness and toxicity of BC819/ [132]. BC819 was shown in a phase IIb clinical study to suppress new tumour development and ablate signal lesions in persons with intermediate-risk nonmuscle invasive bladder cancer/ [133]. A twofold promoter plasmid incorporating H19 and IGF2P4 regulatory sequences was created to boost treatment

effectiveness. In bladder cancer, the double promoter plasmid outperformed the single promoter expression vector [134,135]. BC819 was utilised to treat pancreatic cancer, ovarian cancer, and heterotopic cancer in addition to bladder cancer [136–138]. In conclusion, combining standard chemotherapy with lncRNA-mediated gene therapy might offer a novel cancer therapeutic strategy. Overall, our findings imply that lncRNA may be a useful tool for cancer detection and therapy.

6. Conclusion

Researchers have been compelled to thoroughly investigate the aetiology of cancer with the emergence of high-throughput array technologies such as microarrays and RNA sequencing. LncRNA dysregulation has been shown in a variety of human malignancies and may be a characteristic of new tumours. Despite increased study into lncRNAs in cancer, the specific role of lncRNAs in carcinogenesis remains uncertain. Cancer metastasis, which is the major cause of mortality in cancer patients, is aided by lncRNAs. This review focuses on the role of lncRNA in cancer metastasis. lncRNAs contribute to cancer spread through interactions with miRNAs, epigenetic gene regulation, and EMT progression. Finally, we consider the use of lncRNA as a cancer diagnostic and therapeutic marker. As a result, further study is needed to better understand the function of cancer-specific lncRNAs in cancer development. Integrating lncRNA biology with cancer biology might lead to a better knowledge of cancer metastasis paths in the future, as well as novel applications for efficient, fast, and targeted diagnostics and therapeutics.

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